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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/995,475	11/28/2001	Lewis B. Schwartz	27373/37922	2320

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EXAMINER	
SALIMI, ALI REZA	
ART UNIT	PAPER NUMBER
1648	8

DATE MAILED: 02/27/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/995,475	Applicant(s) Schwartz et al
	Examiner A. R. SALMI	Art Unit 1648

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *1/30/03, 1/28/03* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-33* is/are pending in the application.

4a) Of the above, claim(s) *2, 3, and 15-33* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1 and 4-14* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *4, 7*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Election/Restriction

Applicant's election with traverse of Group II (claims 1, and 4-14) in Paper No. 6 is acknowledged. The traversal is on the ground(s) that the examiner did not supply any reasons in support of the restriction requirements and further assert no burden is required to examined the various groups. In addition, applicants assert that claim 15 should be included since the said claim merely further limits the herpes simplex virus that is administered. This is not found persuasive because, first, the separate classification of the subject matter is a prima facie showing of burden, which is not overcome by applicants' assertion to the contrary. Applicants provide no argument that various groups are not distinct one from the other. In addition, applicants read limitations into claims that are simply not present. The limitation of claim 15 is directed to treatment of herpes virus infection, which is directed to a vaccine. Is the product of claim 1 going to cause herpesvirus infection? There is no limitation present in claim 1 which says the vector is sensitive to antiviral agents and that is the limitation that would disable the vector or a TK gene is present. Applicants reading limitations into the invention that is not recited.

The requirement is still deemed proper and is therefore made FINAL.

Claims 2-3, 15-33 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected Groups. Applicant timely traversed the restriction (election) requirement in Paper No. 6. Claims 1, 4-14 are considered.

Applicants are reminded to cancel the claims to the non elected claims.

Claim Rejections - 35 USC § 112

Claims 1, 4-14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: the regions where the heterologous gene is/are inserted, what is being treated, what gene is being deleted, what is being measured, or how the expression is determined, etc.... This affects the dependent claims.

Claims 9-11 are vague and indefinite the intended "polypeptide", "antisense", is/are not defined. The intended metes and bounds of the polypeptides or antisense is not defined.

Claim Rejections - 35 USC § 112

Claims 1, 4-14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of utilizing a defective herpes simplex virus, wherein the herpesvirus genome lacks both gamma 34.5 genes, wherein the herpesvirus to express a reporter gene into a vascular layers where the vascular region has no prior endothelium injury in an *in vivo* rabbit model only, and/or in an *in vitro* vascular cell culture system, does not reasonably provide enablement for expression of any and all heterologous genes in any and all regions in an *in vivo* model. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. At the onset applicants are reminded that this field is considered to be highly unpredictable and as such the specification should provide adequate teaching for one of ordinary skill in the art to enable the full scope of the invention, absent undue experimentations. The specification does not provide adequate teaching regarding the complications that might be associated with administration of the herpesvirus expression vector within the scope of the invention. Applicants have utilized a rabbit model. The Office is not aware that animal model provided in the specification is the correct model within the scope of the invention. The appropriate model should be a model wherein the same disease can be replicated in that model. Does the rabbit model harbor latent herpesvirus in its cells? If the answer is, No, then one cannot reasonably conclude that the possibility of the recombination may not take place upon administration of the claimed expression vector where the cells may already be infected with

herpesvirus. In other words a full blown herpesvirus infection would take place. Hence, the safety concerns raised would require one of ordinary skill in the art to conduct large quantity of undue experimentations to enable the full scope of the claimed invention. Still further, the breadth and scope of claims read on Gene Therapy, applicants are reminded that the field of Gene Therapy is a highly unpredictable field and the applicant has not shown that the viral vector of the invention is able to render the positive results envisioned by the applicant. To support the above statement the article by Verma et al (Nature, 1997) see page 241, last paragraph, is worth noting regarding the unpredictability of the field and lack of sustained expression of the therapeutic genes. Applicants are directed to further evidence by Smith AE (The Lancet, 1999, vol. 354 suppl. 1, pp 1-4, see page 3, right column). There are no teaching regarding this subject matter with regard to selective effect, sustained delivery and expression of a therapeutic gene. For instance as stated above it is not clear how can the HSV-1 of the invention get to be delivered to the intended cells and not complement with HSV-1 that may be present in a cell to induce a full blown infection? Simple expression of β-gal does not constitute written description within the scope of the claimed invention. The β-gal expression is not equivalent to a therapeutic gene, anti sense, antiporliferative polypeptide, etc... Utilizing a well disclosed vector as taught by Pyles et al (WO 98/42195) and express a marker gene in cells is not equivalent and adequate teaching given the scope of the claimed invention. The β-gal does not have the same pattern of signaling as let say a lymphokine gene. The signaling cascade of a therapeutic agent such as IL-2 or TNF or a tumor associated antigen is entirely different pattern than a simple expression of β-gal gene. The results

of β-gal gene can not be extrapolated to a therapeutic gene. There will a massive immune response against the expression vector. In addition, the state of the art indicates that sustained β-gal causes toxicity, see Detrait et al, Molecular Therapy, 2002, Vol. 5, No. 6, pp. 723-730. The scope of the claims are directed to gene therapy in all hosts including humans, Applicants have general statements regarding the expression of a foreign gene in a vascular cell. However with regard to an unpredictable field, this does not constitute an adequate disclosure. See Fiers v. Revel (25USPQ2d 1601 at 1606; and also decision by the Federal Circuit with regard to the enablement issues see Genentech Inc. v. Novo Nordisk A/S, 42 USPQ2d 1001-1007). For example, the CAFC stated that "It is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of an invention in order to constitute enablement." (See page 1005 of the decision). In the instant case the specification does not teach or provide any guidance for a gene therapy method for utilizing herpes virus vector for expression of any and all genes in all hosts. This means that the disclosure must adequately guide the art worker to determine, without undue experimentation. The applicant can not rely on the knowledge of those skilled in the art to enable the claims without providing adequate teaching. Therefore, considering large quantity of experimentation needed, the unpredictability of the field, the state of the art, and breadth of the claims, it is concluded that undue experimentation would be required to enable the intended claim. Many of these factors have been summarized *In re Wands, 858 F.2d 731, USPQ2d 1400 (Fed. Cir. 1988).*

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 4-14 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Coffin et al (Gene Therapy, 1996, Vol. 3, pp. 560-566).

The teaching of the above cited art meets the broad limitations of the claims 1, 4, 6-9. Coffin et al taught utilization of a herpes simplex virus vector having deletion of 34.5 gene and wherein the vector was utilized in expression of a marker gene into vascular cells (see the abstract, and page 561, right column, 2nd paragraph). Alternatively, one of ordinary skill in the art at the time of filing would have been motivated to delete the second copy of the 34.5 gene to reduce cytotoxicity caused by the virus and to express a foreign gene into vascular cells for treatment of disease as taught by Coffin et al (see page 560, left column, 1st paragraph). The

cited art also taught the expression of marker gene into vascular cells utilizing an attenuated herpesvirus vector. Therefore, one of ordinary skill in the art being familiar with the teaching of Coffin et al would not have anticipated any unexpected result as none have been provided. Applicants are reminded that no unexpected results have been provided with respect to broad limitations of polypeptides or antisense. Hence, the invention as a whole is prima facie obvious absent unexpected results.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 4-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pyles et al (WO 98/42195), and Coffin et al (WO 98/04726).

The claims are directed to method of expressing a general foreign nucleic acid in any and all vascular cells utilizing herpesvirus vector.

Pyles et al detailed a general preparation of herpes virus vector wherein the vector is omitted for gamma 34.5 genes and wherein the vector is sensitive to antiviral agents (see the

claims). In addition, they also taught that the vector can replicate in cells other than nervous tissue origin (see page 4, lines 12-13). Still further, they taught the employment of the vector in gene therapy for expressing foreign genes to kill tumor cells. This only differs since they did not specifically express their vector into vascular tissue.

Coffin et al taught utilization of herpesvirus expression vector having deletion of 34.5 and a functional deletion of ICP27 gen in all types of tissues including vascular tissue (see the abstract, and page 4, lines 7-10). This differs since they did not teach delation of both 34.5 genes. Therefore, one of ordinary skill in the art at the time of fling would have been highly motivated by the above cited art to take the vector taught by Pyles et l and express a marker gene into a vascular tissue as taught by Coffin et al. Each and very element of the claimed invention is taught in the prior art, and one bing familiar with the above cited art would not have anticipated any unexpected results. Applicants are reminded that the skill level is considered high in this art. Taking a well characterized vector as taught by Pyles et al and administering the vector into a rabbit model and observing a marker gene is not considered unexpected results. Therefore, the invention as a whole is prima facie obvious absent unexpected results.

No claims are allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to A. R. Salimi whose telephone number is (703) 305-7136. The examiner can normally be reached on Monday-Friday from 9:00 Am to 6:00 Pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel, can be reached on (703) 308-4027. The fax phone number for this Group is (703) 305-3014, or (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

A. R. Salimi

2/20/2003